215 Analysis of polypharmacy in patients with mild CF lung disease assigned to placebo in phase 3 clinical trial of denufosol

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Introduction: Current treatment of CF lung disease involves a number of inhaled, intranasal, oral and IV medications. We describe the concomitant medication (CM) use in placebo (PL) recipients during a phase 3 trial of denufosol.
Methods: A Phase 3, multicenter, randomized, double-blind, PL-controlled trial was conducted at 62 CF centers in N. America in CF patients (pts) who were clinically stable on entry, $\geqslant$5 yrs of age and with FEV_1 $\geqslant$75% pred. Stable chronic treatments were allowed (except hypertonic saline) and tracked at all visits. Pts were randomized to denufosol (60 mg) or PL (normal saline) inhalation TID for 24 weeks.
Results: From a total of 352 pts, 175 received PL during the 24-week double-blind phase of the study. Among these pts, the mean age was 14.8 years. The mean FEV_1 % pred. was 92%, the mean FEF_{25-75} % pred. was 84%, and the percentage of pts with *P. aeruginosa* in respiratory cultures was 48%. PL-treated pts used the following classes of CMs: selective SABAs (91%), selective LABAs (41%), mucolytics (primarily dornase alfa) (78%), chronic oral macrolides (41%), inhaled antibiotics (54%), IV antibiotics (10%), inhaled corticosteroids (55%), oral corticosteroids (19%), intranasal corticosteroids (58%) and oral leukotriene modifiers (27%). Overall, at least 50% of PL-treated pts used at least 5 CMs for the treatment of their CF lung disease.
Conclusion: Pts with CF face a large treatment burden. New disease modifying treatments that address the basic defects of CF lung disease may reduce the need for the extensive polypharmacy now addressing disease related complications.

216* Clinical features and outcomes of cystic fibrosis pulmonary exacerbations presenting with normal inflammatory markers

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Introduction: Pulmonary exacerbations (PE) are a frequent event in cystic fibrosis (CF) and responsible for much of the diseases morbidity. Whereas the majority of PE are characterized by elevated inflammatory markers (IM), a subset of exacerbations diagnosed on clinical grounds present with low IM.
Objectives and Methods: To determine if there are differences in the clinical characteristics and outcome of those PE associated with normal IM. Admission serum C-reactive protein (CRP) measurements of $\leqslant$10 kg/dl were defined as PE with normal inflammatory markers.
Result: 237 patients were followed from 2006 to 2008 and experienced 628 episodes of PE. Of the 131 patients who experienced exacerbations, 91 patients had 228 PE characterized by CRP < 10. Baseline mean FEV_1 (in the previous 3 months) was higher in patient with CRP < 10 (55.3% predicted vs 47.1%, $p < 0.001$). CRP < 10 PE episodes were more likely to occur in individuals who chronically failed to culture CF pathogens with risk ratio (RR) 1.84 and less likely to occur in individuals chronically infected with *B. cepacia* RR0.42. CRP < 10 PE were characterized by a less severe decline in FEV_1 at admission [–6.2% vs –8.6%, $p = 0.0005$]. Treatment duration was shorter for CRP < 10 PE, 12.5 days vs 14.6, $p = 0.002$. However, improvement of FEV_1 post-treatment was lower in the CRP < 10 group, +8.9% vs +10.9%, $p = 0.01$.
Conclusion: PE characterized by subjective symptoms but normal IM are common in CF especially in those individuals with milder disease. While typically managed with the same aggressive therapy, these interventions fail to produce the same magnitude of improvement in lung function at treatment completion.

217* Monitoring of young children with CF

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Introduction: Close monitoring of CF patients is necessary to improve outcome. For children aged 0–4 years, currently used routine lung function tests are cumbersome or not feasible. It is therefore important to develop alternative methods to assess pulmonary disease. Lung Clearance Index (LCI), nightly oxygen saturation (SpO_2), and/or cough audiometry might be valuable tools in the monitoring of CF patients.
Aim: To compare LCI, overnight SpO_2 and cough in CF patients aged 0–4 years old with a group of healthy controls.
Methods: Prospective cross sectional study. Children with CF were recruited from the outpatient clinic. Healthy children were recruited from child day care facilities. LCI was measured by the Exhalyzer® D at the outpatient clinic. Nightly SpO_2 was measured by the Novametrix Model 2001 MARS pulse oximeter and nightly cough was measured with an audiometer. Both were measured at home during a normal night sleep. We aim to complete inclusion of 20 CF patients and 30 healthy children by April 2010.
Results: To date 38 subjects were included: 18 CF patients (mean age 2.6 yrs) and 20 healthy children (mean age 2.8 yrs). In this abstract we report preliminary data. Age, sex, height and weight were not significantly different between both groups. LCI was higher in CF patients than in healthy children: mean LCI was 8.13 in CF patients and 7.09 in healthy children ($p = 0.03$). For nightly oxygen saturation and for cough no significant differences were found in this preliminary analysis.
Conclusions: LCI showed a clear difference between healthy children and CF patients at a young age. This suggests that LCI is a sensitive test to detect pulmonary changes at an early stage.

218* Ventilation inhomogeneity correlates with airway colonization in patients with CF

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Background: Lung clearance index (LCI), a measure of ventilation distribution and small airway dysfunction derived from multiple breath inert gas washout (MBW) detects lung damage in CF more readily than other pulmonary function tests. Thus, previous studies have shown abnormal LCI among CF patients with chronic gram-negative bacterial airway infection.
Methods: Cross-sectional, retrospective study. Forty-five CF patients aged 5 to 18 yrs participated in the study. LCI was derived from MBW using mass spectrometry and SF_6 as inert gas. Results of monthly sputum cultures the previous year were extracted from CF-database. All were in stable condition with no signs of exacerbation at time of test.
Results: Median FEV_1 was 94% predicted (51% to 133%) and median LCI was 8.5 (6.2 to 13.7). In total 7/44 (16%) had FEV_1 < 80% predicted and 37/45 (82%) had abnormal LCI (>7.17). LCI, but not FEV1 % predicted, correlated to number of positive respiratory cultures over the previous year (r^2=0.524, $p < 0.001$). Patients with frequent positive culture with *S. aureus* had highest LCI levels ($p < 0.005$), Twelve subjects were chronically or intermittently infected with gram-negative bacteria (*S. maltophilia* 4, *P. aeruginosa* 7 and A. xylosoxidans 1), but there was no impact of gram-negative infection status on LCI. Furthermore, no significant influence on LCI by any positive airway culture on day of test was demonstrated.
Conclusion: Small airway dysfunction detected by MBW was, despite normal spirometry, significantly related to recurrent infection, particularly with *S. aureus* in children with CF. Further studies in larger numbers are needed to assess possible causal relationship.